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Office of Surveillance and Epidemiology**

**Pediatric Postmarket Pharmacovigilance and Drug Utilization Review**

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## EXECUTIVE SUMMARY

The Office of Surveillance and Epidemiology (OSE) evaluated postmarket reports of adverse events, and drug utilization data with clopidogrel bisulfate in pediatric patients (0-17 years of age) in accordance with Best Pharmaceuticals for Children Act (BPCA).

Clopidogrel bisulfate is a P2Y<sub>12</sub> platelet inhibitor approved by the FDA on November 17, 1997. Clopidogrel bisulfate is indicated in the adult population for:

- Prevention of vascular ischemic events in patients with symptomatic atherosclerosis
- Acute coronary syndrome (ACS) without ST-segment elevation (NSTEMI)
- ST-elevation MI (STEMI)

Pursuant to a Pediatric Written Request (PWR), clopidogrel was studied in neonates or infants for use in the reduction of the incidence of thrombosis in children with systemic-to-pulmonary artery shunts (STPAS) for palliation of cyanotic congenital heart disease (CCHD). A randomized, placebo-controlled trial (CLARINET) did not demonstrate a clinical benefit of clopidogrel in neonates and infants with CCHD palliated with STPAS. Clopidogrel bisulfate is not indicated for use in the pediatric population.<sup>1</sup>

The FDA Adverse Event Reporting System (FAERS) database was searched for all reports of adverse events (serious and non-serious) from approval (November 17, 1997) to March 22, 2013. FAERS contained 14,961 reports of clopidogrel bisulfate. Pediatric reports represent approximately 0.3% of the total (44/14,961). After removing duplicate reports and reconciling null age death values, we identified 18 serious pediatric cases associated with clopidogrel, which included 4 deaths and 14 non-fatal post-marketing cases.

Of the 4 deaths, two patients were enrolled in the CLARINET study. One case reported shunt occlusion in a 5-month old due to underlying cardiac disease who died from complications of surgery. A second case reported a 1-month old who died of cardiac arrest following post-procedural hemorrhage during surgery. A third case reported heparin induced thrombocytopenia and thrombosis (HIT II) which contributed to a 13 month-old patient's death following multi-organ failure, but clopidogrel was added after the reaction occurred. The remaining case from a foreign source reported cerebral hemorrhage in a 2.5-month old, but the cause of death was unknown due to lack of information in the report. Accordingly, all death cases were related to other etiologies, not directly attributable to clopidogrel.

Of the 14 non-fatal serious outcome cases:

- Two cases reported accidental overdose of clopidogrel with higher than intended doses, but neither patient experienced an adverse event.
- Two cases reported accidental ingestion of clopidogrel with multiple medications reported in one case, but neither patient experienced an adverse event.
- One case reported intentional overdose from multiple medications including clopidogrel. The patient experienced cardiac arrest, but recovered without sequelae.
- Two cases reported device related thrombosis with one case occurring prior to clopidogrel and the other case lacking sufficient information for assessment, however the event resolved with increasing clopidogrel dose.
- Two cases reported bleeding from concomitant use of anticoagulation drugs such as ASA or warfarin.

- Two cases reported lethargy with an underlying feeding disorder and confusional state that could have been attributed to underlying cardiac and other hereditary diseases.
- One case reported unilateral deafness and tinnitus with no resolution of symptoms upon clopidogrel cessation.
- One case reported respiratory arrest attributable to underlying aspiration.
- One case reported oropharyngeal blistering and oropharyngeal pain with a possible relationship to clopidogrel, however the events are well-described in clopidogrel labeling.

In order to provide context, drug utilization patterns for U.S. non-federal hospital and outpatient retail pharmacy settings were assessed. In the U.S. non-federal hospital setting, approximately 2.2 million total patients were billed for clopidogrel during an inpatient or outpatient ER stay in year 2012 of which the off-label use in the pediatric population aged 0-16 years accounted for less than 1% of use (581 patients). In the U.S. outpatient retail pharmacy setting, approximately 4.2 million total patients received a dispensed prescription for clopidogrel in year 2012. Similar to hospital utilization, the off-label use in the pediatric population aged 0-16 years accounted for less than 1% of use (9,000 patients). From 2002 through 2012, hospital pediatric use slightly decreased, whereas outpatient pediatric use nearly tripled during the 11 year time period.

DPV identified no new safety concerns with the use of clopidogrel. DPV will continue to monitor adverse events reported with clopidogrel use.

## 1 INTRODUCTION

In accordance with BPCA, the Division of Pharmacovigilance (DPV) was asked to summarize post-marketing reports of adverse events associated with the use of Plavix (clopidogrel bisulfate) in pediatric patients (0-17 years of age). The main focus of this review is pediatric deaths and pediatric reports of serious unlabeled adverse events with clopidogrel.

### 1.1 PEDIATRIC REGULATORY HISTORY<sup>2</sup>

Plavix was first approved in 1997 for treatment of ACS in adults. Pursuant to a PWR, studies in neonates (age < 1 month), and infants/toddlers (age 1-24 months) were performed with focus in the reduction of the incidence of thrombosis in children with STPAS for palliation of CCHD. Three key studies in the pediatric development program are summarized below:

To establish an age-appropriate formulation, the sponsor conducted a single-dose oral bioavailability study in 24 healthy male volunteers age 18-40 years, comparing an aqueous clopidogrel solution (75 mg) to a commercial Plavix 75 mg tablet. The data indicated that the point estimate for the solution  $C_{max}$  was 15% higher and the  $t_{max}$  was 15 minutes sooner than for the tablet.

The sponsor also conducted a pharmacodynamic dose-finding study entitled Platelet Aggregation Inhibition in Children On Clopidogrel (PICOLO), was a randomized, double-blind, placebo-controlled Phase 2 study which enrolled 92 patients (neonates and infants/toddlers) at 22 centers in 6 countries in North America and Western Europe. The primary objective of this study was a pharmacodynamic assessment to determine the dose of clopidogrel to achieve a mean 30 to 50% inhibition of 5 $\mu$ M ADP-induced platelet aggregation in neonates or infants/toddlers at risk for thrombosis. Though the planned doses for assessment were 0.01, 0.1 and 1.0 mg/kg, the highest dose tested was 0.2 mg/kg, because the platelet aggregation with the 0.1 mg/kg dose was already approaching target levels.

These efforts led to a study entitled Efficacy And Safety Of Clopidogrel In Neonates/Infants With Systemic To Pulmonary Artery Shunt Palliation (CLARINET). This was a randomized, placebo-

controlled, double-blind trial assessing the effects of clopidogrel 0.2 mg/kg/day by mouth or feeding tube on a composite endpoint of death and thrombotic complications in neonates and infants/toddlers with CCHD who were surgically treated with STPAS. Results showed no statistically significant safety or efficacy differences between the treatment arms.

Despite concerns that two of the formulations used in the pediatric studies were not evaluated for bioavailability, and were potentially inadequate to show a difference between clopidogrel and placebo (and no difference was observed), pediatric exclusivity was nonetheless granted in January, 2011, as noted in the Medical Officer's review where much of this information was collected.<sup>2</sup>

## **1.2 HIGHLIGHTS OF LABELED SAFETY ISSUES<sup>1</sup>**

### **CONTRAINDICATIONS**

Active pathological bleeding, such as peptic ulcer or intracranial hemorrhage. Hypersensitivity to clopidogrel or any component of the product.

### **WARNINGS AND PRECAUTIONS**

Reduced effectiveness in impaired CYP2C19 function: Avoid concomitant use with omeprazole or esomeprazole. Bleeding: Plavix increases risk of bleeding. Discontinue 5 days prior to elective surgery. Discontinuation of Plavix: Premature discontinuation increases risk of cardiovascular events. Recent transient ischemic attack or stroke: Combination use of Plavix and aspirin in these patients was not shown to be more effective than Plavix alone, but was shown to increase major bleeding. Thrombotic thrombocytopenic purpura (TTP): TTP has been reported with Plavix, including fatal cases.

### **ADVERSE REACTIONS**

Bleeding, including life-threatening and fatal bleeding, is the most commonly reported adverse reaction.

### **DRUG INTERACTIONS**

Nonsteroidal anti-inflammatory drugs (NSAIDs): Combination use increases risk of gastrointestinal bleeding. Warfarin: Combination use increases risk of bleeding.

### **USE IN SPECIFIC POPULATIONS**

Nursing mothers: Discontinue drug or nursing, taking into consideration importance of drug to mother.

### **PEDIATRIC USE**

Safety and effectiveness in pediatric populations have not been established. A randomized, placebo-controlled trial (CLARINET) did not demonstrate a clinical benefit of clopidogrel in neonates and infants with cyanotic congenital heart disease palliated with a systemic-to-pulmonary arterial shunt. Possible factors contributing to this outcome were the dose of clopidogrel, the concomitant administration of aspirin and the late initiation of therapy following shunt palliation. It cannot be ruled out that a trial with a different design would demonstrate a clinical benefit in this patient population.

## 2 POSTMARKET ADVERSE EVENTS

### 2.1 METHODS AND MATERIALS

#### 2.1.1 FDA Adverse Event Reporting System (FAERS) Search Strategy

The FAERS database was searched with the strategy described in Table 2.1.1. See Appendix A for a description of the FAERS database.

**Table 2.1.1 FAERS Search Strategy**

Date of search	March 28, 2013
Time period of search	November 17, 1997 <sup>*</sup> to March 22, 2013
Product Name(s)	Plavix, clopidogrel, clopidogrel bisulfate, clopidogrel/clopidogrel bisulfate
Search Parameters	Age 0 to 17.99 years
<sup>*</sup> US approval date	

### 2.2 RESULTS

#### 2.1.2 FAERS Data Summary

**Table 2.2.1 Adult and pediatric FAERS cases\* from November 17, 1997 to March 22, 2013 with clopidogrel**

	All reports (US)	Serious <sup>†</sup> (US)	Death (US)
Adults (≥ 18 years)	14,913 (7956)	13,925 (7246)	2611 (1190)
Pediatrics (0-17 years)	48 (28)	44 <sup>‡</sup> (25)	7 <sup>§</sup> (5)

\* May include duplicates and have not been assessed for causality

<sup>†</sup> Serious adverse drug experiences per regulatory definition (CFR 314.80) include outcomes of death, life-threatening, hospitalization (initial or prolonged), disability, congenital anomaly, and other serious important medical events.

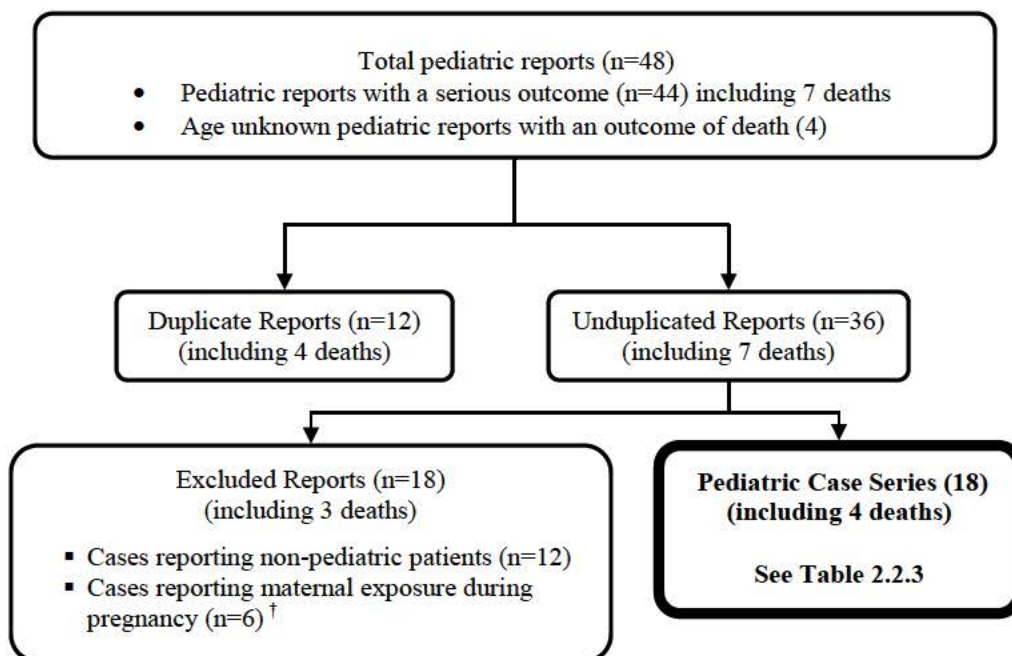
<sup>‡</sup> See Figure 2.2.1

<sup>§</sup> N=4 additional cases of pediatric deaths were identified among cases not reporting an age

### 2.1.3 Selection of Serious Pediatric FAERS Cases

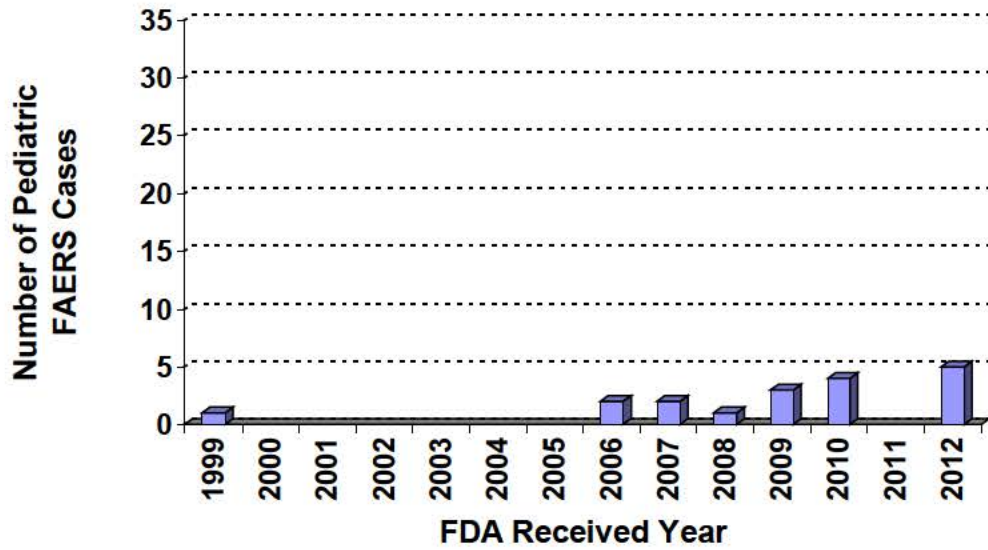
We identified 48 pediatric reports with a serious outcome (See Table 2.2.1). **Figure 2.2.1** below summarizes the specific selection of cases to be reviewed in **Section 4**

**Figure 2.2.1 Selection of Serious Pediatric FAERS Cases with clopidogrel**



<sup>†</sup> Excluded reports (pre-consult meeting discussion 03/07/13)

**Figure 2.2.2 Serious Pediatric Cases Series for clopidogrel, by year of FDA receipt (November 17, 1997 to March 22, 2013)(n=18)**



## 2.1.4 Pediatric Case Series Summary

Table 2.2.3 summarizes the 18 FAERS cases from the Pediatric Case Series with clopidogrel.

<b>Table 2.2.3 Descriptive Characteristics of Pediatric Case Series with clopidogrel</b>		
<b>(N=18)</b>		
Age	0 - 1 month	0
	1 month - <2 years	11
	2-5 years	2
	6-11 years	1
	12-17 years	4
Sex	Male	9
	Female	6
	Unknown	3
Country of reporter	United States	11
	Foreign	7
Serious Outcomes (non-mutually exclusive)	Death	4
	Life-threatening	5
	Hospitalized	6
	Disability	1
	Congenital anomaly	0
	Other serious	9
Indication <sup>†</sup>	Shunt thrombosis	3
	Anticoagulation	3
	Suicide attempt	1
	Cardiac valve replacement	2
	Coronary stent placement	1
	ASD	1
	PFO closure	1
	Narrow arteries	1
	Unknown	5

<sup>†</sup> ASD= atrial septal defect, PFO= patent foramen ovale

## 3 DRUG UTILIZATION DATA

### 3.1 METHODS AND MATERIALS

#### 3.1.1 Determining Settings of Care

The IMS Health, IMS National Sales Perspectives™ database (see Appendix 8.2 for database descriptions) was used to determine the various retail and non-retail channels of distribution for clopidogrel. Sales data for year 2012 indicated that approximately 73% of clopidogrel bottles were distributed from manufacturers to outpatient retail pharmacies, 21% to mail-order/specialty pharmacies, and 6% to non-retail settings.<sup>1</sup>

<sup>1</sup> IMS Health, IMS National Sales Perspectives™ Database. Year 2012. Extracted March 5, 2013. File: NSP 2013-910 Clopidogrel BPCA Y2012, 3-28-2013.xls.

Non-federal hospital and outpatient retail drug utilization databases were used to provide a comprehensive analysis on pediatric drug use patterns for clopidogrel. Mail-order/specialty pharmacy and clinic data were not included in this analysis.

### ***3.1.2 Data Sources Used***

Proprietary drug use databases were used to conduct this analysis. Detailed descriptions of the databases are included in Appendix 8.2.

The IMS, Inpatient Healthcare Utilization System (IHCaUS) database was used to obtain the nationally estimated number of discharges and patients with a hospital billing for clopidogrel from the inpatient and outpatient ER settings of U.S. non-federal hospitals, stratified by patient age groups (<1 year, 1-5 years, 6-16 years, and 17 years and older) from years 2002 through 2012.

The IMS, Vector One®: National (VONA) and Total Patient Tracker (TPT) databases were used to obtain the nationally estimated number of prescriptions dispensed and the number of patients who received a dispensed prescription for clopidogrel from U.S. outpatient retail pharmacies, stratified by patient age groups from years 2002 through 2012. The top prescribing specialties associated with the use of clopidogrel were also obtained from the IMS, Vector One®: National (VONA) database.

The Encuity Research, LLC, Treatment Answers™ database was used to obtain information on the diagnoses associated with the use of clopidogrel as reported by U.S. office-based physician survey, stratified by patient age groups, from years 2002 through 2012, cumulative.

## **3.2 RESULTS**

### ***3.2.1 Non-Federal Hospital Utilization: Patient and Discharge Data***

**Tables 1 and 2 in Appendix 8.3** provide the nationally estimated number of patients and discharges with a hospital billing for clopidogrel from U.S. non-federal hospitals, stratified by patient age, from 2002 through 2012. Approximately 2.2 million total patients and 3.4 million total discharges were billed for clopidogrel during an inpatient or outpatient ER hospital stay in year 2012. The adult population aged 17 years and older accounted for the vast majority of hospital utilization at 99.9% (2.2 million patients and 3.4 million discharges) of total use. The pediatric population aged 0-16 years accounted for less than 1% (581 patients and 621 discharges) of total use. Among the pediatric population, patients aged 6-16 years accounted for the majority of use at approximately 57% (332 patients) of pediatric patients in year 2012. Patients aged less than 1 year accounted for 21% (121 patients and 129 discharges) of pediatric use in year 2012.

The annual number of total patients with a hospital billing for clopidogrel increased by 26% from approximately 1.8 million patients in year 2002 to 2.2 millions patients in year 2012. **Figure 1 in Appendix 8.3** shows the annual number of pediatric patients aged 0-16 years slightly decreased by 2% from 595 patients in year 2002 to 581 patients in year 2012, with a peak in year 2009 of approximately 1,000 patients. In general, trends for discharge data were similar to those of patient data.

### ***3.2.2 Outpatient Retail Utilization: Patient and Prescription Data***

**Tables 3 and 4 in Appendix 8.3** provide the nationally estimated number of prescriptions and patients who received a dispensed prescription for clopidogrel from U.S. outpatient retail pharmacies, stratified by patient age, from 2002 through 2012. Approximately 22.8 million prescriptions were dispensed and 4.2 million total patients received a dispensed prescription for clopidogrel in year 2012. Similar to hospital utilization data, the adult population aged 17 years and older accounted for the vast majority of patients,

with approximately 99.8% (4.2 million patients) of total patients. The off-label use in the pediatric population aged 0-16 years accounted for less than 1% (9,000 patients) of total patients and prescriptions (24,000 prescriptions). Among the pediatric patients who received a dispensed prescription for clopidogrel, the largest proportion of use were for patients aged 6-16 years accounting for approximately 74.5% (6,000 patients) of pediatric patients. Patients aged less than 1 year accounted for approximately 5% (462 patients) of pediatric patients in year 2012.

Overall, the total number of patients who received a prescription for clopidogrel increased by 53% from approximately 2.7 million patients in year 2002 to 4.2 million patients in year 2012. **Figure 2** in **Appendix 8.3** shows the number of pediatric patients aged 0-16 years who received a prescription for clopidogrel increased by 3-fold from approximately 3,000 patients in year 2002 to 9,000 patients in year 2012. Trends in dispensed prescriptions data were similar to patient data for outpatient retail pharmacy settings during the examined time.

### 3.2.3 Prescriber Specialty

**Table 5** in **Appendix 8.3** provides the top 15 prescribing specialties for clopidogrel by the nationally estimated number of prescriptions dispensed from U.S. outpatient retail pharmacies, from 2002 through 2012, cumulative. Cardiology was the top prescribing specialty accounting for approximately 28% (64.2 million prescriptions) of clopidogrel prescriptions. Pediatricians accounted for less than 1% (1.7 million prescriptions) of total dispensed prescriptions.

### 3.2.4 Diagnoses Associated with Use

**Table 6** in **Appendix 8.3** provides the top diagnoses associated with the use of clopidogrel, as reported by U.S. office-based physician surveys, stratified by patient age, from 2002 through 2012, cumulative. Physician diagnoses were coded according to the International Classification of Disease (ICD-9 codes) and 95% confidence intervals were applied to the estimates. For the adult population aged 17 years and older, “Coronary Atherosclerosis” was the top diagnosis associated with the use of clopidogrel, accounting for approximately 25% of drug use mentions.

Among pediatric patients, “History of Circulatory Disease” was the top diagnosis associated with the use of clopidogrel in patients aged 6-16 years with approximately 64% or 19,000 drug use mentions (95% CI, <500 – 39,000). However, the diagnosis codes reported in the pediatric age groups were below the acceptable count allowable to provide a reliable estimate of national use, and the results must therefore be interpreted with caution as the sample size was very small with correspondingly large confidence intervals. ***In addition, no drug use mentions associated with the use of clopidogrel in pediatric patients aged 0-5 years were captured in the physician survey data.***

## 3.3 LIMITATIONS AND SUMMARY

In the U.S. non-federal hospital setting, the pediatric population aged 0-16 years accounted for less than 1% of use (581 patients and 621 discharges) of the approximately 3.4 million total discharges and 2.2 million total patients who were billed for clopidogrel during an inpatient or outpatient ER stay in year 2012. Similarly, in the U.S. outpatient retail pharmacy setting, the pediatric population also accounted for less than 1% of use (9,000 patients and 24,000 prescriptions) of the approximately 22.8 million prescriptions and 4.2 million patients who received a dispensed prescription for clopidogrel. From 2002 through 2012, hospital pediatric use slightly decreased, whereas outpatient pediatric use nearly tripled during the 11 year time period. Outpatient diagnosis codes reported by office-based physician survey data for pediatric use of clopidogrel were small and may not be representative of national pediatric use.

Findings from the drug utilization analysis should be interpreted in the context of the known limitations of the databases used. We estimated that clopidogrel products were distributed primarily to the outpatient retail pharmacy setting based on sales data for year 2012. To provide a comprehensive analysis on

pediatric drug use patterns for clopidogrel, we conducted our analysis of use in the outpatient retail pharmacy settings, and in the inpatient and outpatient ER non-federal hospital settings; therefore, these estimates may not apply to other settings of care in which these products are used (mail-order, clinics). The estimates provided are national estimates, but no statistical tests were performed to determine statistically significant changes over time or between products. Therefore, all changes over time or between products should be considered approximate, and may be due to random error.

## **4 DISCUSSION**

### **4.1 PEDIATRIC DEATHS (N=4)**

Four cases reported an outcome of death with use of clopidogrel. The median age was 4 months ranging from 1 month to 13 months. Gender was specified in four cases including males (3) and female (1). There were domestic (2) and foreign (2) reports. Two cases reported duration of therapy of two days (1) and twelve weeks (1).

Four cases reported vascular adverse events including shunt thrombosis (1), puncture site hemorrhage (1), heparin induced thrombocytopenia and thrombosis (1) and cerebral hemorrhage (1). Two patients were enrolled in a randomized double-blind clinical study evaluating the efficacy and safety of clopidogrel once daily versus placebo for the reduction of all-cause mortality and shunt-related morbidity in neonates and infants with CCHD palliated with STPAS (CLARINET):

- The first case reported occlusion of a modified Blalock-Taussig shunt (MBTS) following clopidogrel discontinuation.<sup>3</sup> MBTS to the pulmonary artery (PA) was performed on a 5-month old male due to stenosis of the major aortopulmonary collateral arteries (MAPCA). Clopidogrel was discontinued in preparation for surgery, however the operation was postponed due to viral conjunctivitis. Shunt occlusion occurred during surgery followed by cardiac arrest. Postoperatively, MRI of the brain showed cerebral edema and ischemic damage. The patient died twelve days later.
- In the second case, balloon dilatation of the shunt was performed on a one-month old male after palliation due to worsening tricuspid regurgitation. Post-procedural hemorrhage was diagnosed after perforation of the iliac artery. During surgical repair the patient arrested and died. Clopidogrel was continued throughout the duration of the study.

The third case reported the development of HIT II following Berlin Heart implantation.<sup>4</sup> A 13-month old female with Shone's anomaly underwent ventricular assist device (VAD ) placement pending a heart transplantation. She developed HIT II three days after receiving heparin for anticoagulation. A thrombus was observed on the valve post implantation day ten. Clopidogrel was added to anticoagulation. A second VAD was placed and heparin was discontinued on confirmation of HIT II. Despite the addition of lepirudin, the patient developed pulmonary and gastrointestinal hemorrhage, multi-organ failure and died (care withdrawn).

The remaining case was a study conducted to evaluate information about adverse drug reactions (ADR) in the Spanish pediatric population.<sup>5</sup> One case reported cerebral hemorrhage in a 2.5-month old male following clopidogrel and ASA administration. No additional information was provided.

Please see Appendix D for a detailed summary of the fatal pediatric cases.

*Three deaths were due to complications of underlying disease (2) and surgery (1). One case lacked sufficient clinical detail for assessment. The unlabeled term heparin induced thrombocytopenia and thrombosis appeared to be related to HIT II and occurred prior to clopidogrel administration.*

*The following terms puncture site hemorrhage (1) and cerebral hemorrhage (1) are labeled as “General Risk of Bleeding” in the warnings and precautions section and hemorrhage of operative wound (1) and fatal intracranial bleeding (1), respectively, in the adverse reactions section of clopidogrel labeling. Shunt thrombosis (1) is labeled as “Discontinuation of Plavix: Premature discontinuation of Plavix may increase the risk of cardiovascular events” in the warnings and precautions section of clopidogrel labeling.*

## **4.2 SELECTED NON-FATAL PEDIATRIC SERIOUS ADVERSE EVENTS**

### **4.2.1 OVERDOSE AND ACCIDENTAL EXPOSURE (N=5)**

Five cases reported overdose (3) and accidental exposure (2) with clopidogrel. Median age was 18 months ranging from 4 months to 17 years. Male (3) and female (1) was reported. There were domestic (2) and foreign (3) reports. Two cases reported accidental overdose with no adverse events reported. One case reported intentional overdose involving administration of multiple medications. No adverse events were reported with accidental exposures.

- A four-month old male received clopidogrel 0.2 mg/kg as an oral suspension via a trans-pyloric feeding tube for an artificial heart valve replacement. He was inadvertently given a 37.5 mg dose of clopidogrel which was “thirty times” the intended dose. He did not experience any adverse event. A blood transfusion was given and he was switched to heparin.
- A fourteen-month old female received clopidogrel 0.2 mg/kg “1.6 mg QD = 0.48 ml” for anticoagulation. When admitted, the physician wrote 0.25 tablet instead of dissolve 0.25 tablet (18.75 mg) with 5 ml of water and give 1.6 mg = 0.48 ml. The patient received 18.75 mg of clopidogrel instead of 1.6 mg. The patient did not experience any adverse effects. Clopidogrel was restarted two days later.
- A 17-yo male took acebutolol, lisinopril, simvastatin, clopidogrel, diosmin, alprazolam and permixon in the context of an intentional overdose. The patient experienced cardiac arrest. He recovered without sequelae.
- A 2-yo male was accidentally exposed to the following medications (one dose each): risperidone, metoprolol succinate, clopidogrel, ASA, metformin, torsemide, simvastatin and pantoprazole. The patient did not experience any clinical symptoms. He recovered from the event.
- An 18-month old patient received clopidogrel by mistake. No adverse event was reported.

*Overdose and accidental exposure are unlabeled terms.*

### **4.2.2 VASCULAR (N=4)**

Four cases reported vascular adverse events including thrombosis in device (2), and hemorrhage (2). Median age was four years ranging from 15 months to 15 years. Male (1) and female (1) was reported. All reports were of a domestic origin. One case reported duration of therapy for two months. One of four

cases lacked a temporal relationship to clopidogrel. Another case contained insufficient information for assessment. The remaining cases were confounded by underlying disease or concomitant medications.

- One case reported valve thrombosis in a 17-month old female following warfarin administration after valvular surgery. After multimodal anticoagulation, the patient was placed on clopidogrel (with warfarin). She responded to therapy, however INR values were abnormal.
- The second case reported device thrombosis in a 15-yo patient following clopidogrel administration (indication unspecified). Concomitant medications included warfarin and ASA. The clopidogrel dose was doubled. Device parameters normalized.
- One case reported a 15-month old child who required aggressive multimodal anticoagulation including ASA, dipyridamole, clopidogrel and warfarin after implantation of a Berlin Heart.<sup>6</sup> ASA resistance was detected in the patient. At heart transplantation, the patient experienced coagulopathy following protamine administration. Bleeding ceased following factor VII administration.
- A 7-yo male with a complex medical history of atrioventricular canal defect and Down's syndrome, developed oral cavity bleeding, hematemesis and bruising following clopidogrel administration after a coronary arterial stent insertion. Concomitant medications included ASA and fish oil. Symptoms improved upon clopidogrel and fish oil withdrawal. Clopidogrel dose was increased one year later with worsening of symptoms. The patient's blood work was positive for anti-platelet antibodies (Ia/IIa and IIb/IIIa).

***Hemorrhage is labeled as “General Risk of Bleeding” in the warnings and precautions section of clopidogrel labeling. Thrombosis in device is an unlabeled term. In one case, thrombosis in device occurred prior to clopidogrel administration. The other case lacked sufficient information to assess thrombosis in device, however the event resolved after the clopidogrel dose was increased.***

#### **4.2.3 NERVOUS SYSTEM (N=2)**

Two cases reported nervous system adverse events including lethargy and confusional state.

- A 3.5 month old male with hypoplastic left heart syndrome (HLHS) was enrolled in the CLARINET study. Following surgery, the patient received clopidogrel. He presented with increasing lethargy three months later in the context of a feeding disorder (medication withdrawn one day prior). The patient received balloon angioplasty due to increasing pressure in the aortic arch. Clopidogrel was restarted two days later.
- The second case reported dementia-like symptoms including confusion, memory loss and slurred speech twenty minutes following medroxyprogesterone acetate (MPA) administration in a 16-yo female with dicentric x syndrome. Concomitant medications included clopidogrel, ASA, Synthroid and Vivelle Dot. Symptoms abated upon MPA and clopidogrel withdrawal. PMH was significant for medication sensitivity, narcotic allergies, nasal allergies, migraine headaches, hypothyroidism, ovarian failure and closure of a PFO.

***Confusional state is labeled as “confusion” in the adverse reactions section of clopidogrel labeling. The single case reporting the unlabeled event lethargy was confounded by the patient's feeding disorder and underlying cardiac disease.***

#### **4.2.4 GASTROINTESTINAL (N=1)**

One case reported gastrointestinal adverse events including oropharyngeal blistering and oropharyngeal pain.

- A 2-yo female experienced oral mucosa blistering and sore throat one day following clopidogrel administration after ASD repair. Symptoms resolved upon clopidogrel discontinuation. Concomitant medication included ASA.

***Oropharyngeal blistering and oropharyngeal pain are labeled as erythema multiforme and Stevens-Johnson syndrome in the adverse reactions section of clopidogrel labeling.***

#### **4.2.5 OTIC (N=1)**

One case reported unilateral deafness and tinnitus.

- A 16-yo male experienced tinnitus and hearing loss in the right ear five days after starting clopidogrel for Moyamoya disease. Clopidogrel was discontinued with no resolution in symptoms.

***Unilateral deafness and tinnitus are unlabeled terms; however the events are unlikely drug related as symptoms did not resolve following clopidogrel discontinuation.***

#### **4.2.6 RESPIRATORY (N=1)**

One case reported respiratory arrest.

- A 37-day old female with HLHS was enrolled in a “blinded clinical study”. Following Stage 1 Norwood repair, the patient was hospitalized due to respiratory distress. Lab values revealed respiratory acidosis and hypoxia. Echo showed poor cardiac function, however the patient’s shunt was patent. An upper GI on day five showed gastroesophageal reflux disease (GERD). Respiratory arrest was thought to be due to an aspiration episode. It was unclear if the patient was randomized to clopidogrel or placebo treatment.

***Respiratory arrest is an unlabeled term; however the event was confounded by underlying aspiration.***

### **4.3 EXCLUDED REPORTS**

#### **4.4 PREGNANCY, PUERPERIUM AND PERINATAL CONDITIONS (N=6)**

Six cases reported pregnancy, puerperium and perinatal adverse events including maternal exposure during pregnancy (6). Each case reported different adverse events with no specific patterns of interest. All cases were confounded by underlying disease or concomitant medications. Full cases are described in Appendix F.

## 5 CONCLUSION

We reviewed eighteen pediatric cases reported with clopidogrel use including 4 deaths and 14 non-fatal postmarketing cases. Of the 4 deaths, two patients were enrolled in the CLARINET study. One case reported shunt occlusion in a 5-month old due to underlying cardiac disease who died from complications of surgery. A second case reported a 1-month old who died of cardiac arrest following post-procedural hemorrhage during surgery. A third case reported HIT II which contributed to a 13 month-old patient's death following multi-organ failure, but clopidogrel was added after the reaction occurred. The remaining case from a foreign source reported cerebral hemorrhage in a 2.5-month old, but the cause of death was unknown due to lack of information in the report. Accordingly, all death cases were related to other etiologies, not directly attributable to clopidogrel.

Of the 14 non-fatal serious outcome cases:

- Two cases reported accidental overdose of clopidogrel with higher than intended doses, but neither patient experienced an adverse event.
- Two cases reported accidental ingestion of clopidogrel with multiple medications reported in one case, but neither patient experienced an adverse event.
- One case reported intentional overdose from multiple medications including clopidogrel. The patient experienced cardiac arrest, but recovered without sequelae.
- Two cases reported device related thrombosis with one case occurring prior to clopidogrel and the other case lacking sufficient information for assessment, however the event resolved with increasing clopidogrel dose.
- Two cases reported bleeding from concomitant use of anticoagulation drugs such as ASA or warfarin.
- Two cases reported lethargy with an underlying feeding disorder and confusional state that could have been attributed to underlying cardiac and other hereditary diseases.
- One case reported unilateral deafness and tinnitus with no resolution of symptoms upon clopidogrel cessation.
- One case reported respiratory arrest attributable to underlying aspiration.
- One case reported oropharyngeal blistering and oropharyngeal pain with a possible relationship to clopidogrel, however the events are well-described in clopidogrel labeling.

## 6 RECOMMENDATIONS

DPV identified no new serious safety concerns with use of clopidogrel. DPV will continue to monitor adverse events reported with clopidogrel use.

## 7 REFERENCES

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## **8 APPENDICES**

### **8.1 APPENDIX A. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)**

#### **FDA Adverse Event Reporting System (FAERS)**

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support the FDA's post-marketing safety surveillance program for drug and therapeutic biologic products. The informatic structure of the database adheres to the international safety reporting guidance issued by the International Conference on Harmonisation. Adverse events and medication errors are coded to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. The suspect products are coded to valid tradenames or active ingredients in the FAERS Product Dictionary (FPD).

FDA implemented FAERS on September 10, 2012, and migrated all the data from the previous reporting system (AERS) to FAERS. Differences may exist when comparing case counts in AERS and FAERS. FDA validated and recoded product information as the AERS reports were migrated to FAERS. In addition, FDA implemented new search functionality based on the date FDA initially received the case to more accurately portray the follow up cases that have multiple receive dates.

FAERS data have limitations. First, there is no certainty that the reported event was actually due to the product. FDA does not require that a causal relationship between a product and event be proven, and reports do not always contain enough detail to properly evaluate an event. Further, FDA does not receive reports for every adverse event or medication error that occurs with a product. Many factors can influence whether or not an event will be reported, such as the time a product has been marketed and publicity about an event. Therefore, FAERS data cannot be used to calculate the incidence of an adverse event or medication error in the U.S. population.

## 8.2 APPENDIX B. DRUG UTILIZATION DATABASE DESCRIPTIONS

### **IMS Health, IMS National Sales Perspectives™: Retail and Non-Retail**

The IMS Health, IMS National Sales Perspectives™ measures the volume of drug products, both prescription and over-the-counter, and selected diagnostic products moving from manufacturers into various outlets within the retail and non-retail markets. Volume is expressed in terms of sales dollars, eaches, extended units, and share of market. These data are based on national projections. Outlets within the retail market include the following pharmacy settings: chain drug stores, independent drug stores, mass merchandisers, food stores, and mail service. Outlets within the non-retail market include clinics, non-federal hospitals, federal facilities, HMOs, long-term care facilities, home health care, and other miscellaneous settings.

### **IMS, Inpatient HealthCare Utilization System (IHCareUS)**

The IMS, Inpatient HealthCare Utilization System (IHCareUS) provides hospital inpatient and outpatient emergency department encounter transactions and patient level data drawn from hospital operational files and other reference sources. Encounter information is available from mid-2001, is collected weekly and monthly and is available 25-30 days after the end of each monthly period. This robust data set includes > 650 hospitals with hospital inpatient and outpatient encounter data linked to each appropriate patient as well as to select individual hospital departments by anonymized, consistent, longitudinal patient identifiers. These data include >7 million annual hospital inpatient encounters and >60 million annual hospital outpatient encounters (including ED visits) representing acute care, short-term hospital inpatient sites, and their associated hospital emergency departments in order to measure and track the near term health care utilization of hospitalized patients. Each hospital patient encounter includes detailed drug, procedure, device, diagnosis, and applied charges data as well as location of initiation of each service within the hospital setting of care (e.g. Pediatric, ICU) by day for each patient's entire stay, as well as patient demographics and admission/discharge characteristics. IMS' datasets are geographically representative, and include claims across all third-party payer types, including commercial insurers, Medicare, Medicare Part D, Medicaid and other payer types.

The IMS Hospital Charge Data Master (CDM) sample does not include Federal hospitals, including VA facilities, and some other specialty hospitals, and does not necessarily represent all acute care hospitals in the U.S. in all markets. Caveats of the IMS CDM data source are common to this type of hospital charge information, but are mostly limited to limitations of charge descriptions and what is actually entered by the sample hospitals. However, validations of IMS' Hospital CDM data using both the National Hospital Discharge Survey (NHDS) and the AHRQ HCUP data have shown IMS' patient level data to be representative and accurate across multiple therapeutic areas.

### **IMS, Vector One®: National (VONA)**

The IMS, Vector One®: National (VONA) database measures retail dispensing of prescriptions or the frequency with which drugs move out of retail pharmacies into the hands of consumers via formal prescriptions. Information on the physician specialty, the patient's age and gender, and estimates for the numbers of patients that are continuing or new to therapy are available.

The Vector One® database integrates prescription activity from a sample received from payers, switches, and other software systems that may arbitrage prescriptions at various points in the sales cycle. Vector One® receives over 1.9 billion prescription claims per year, representing over 158 million unique patients. Since 2002 Vector One® has captured information on over 15 billion prescriptions representing over 356 million unique patients.

Prescriptions are captured from a sample from the universe of approximately 59,000 pharmacies throughout the U.S. There are over 800,000 physicians in the VECTOR One database, which supplies VONA, TPT, & DET. The pharmacies in the database account for most retail pharmacies and represent nearly half of retail prescriptions dispensed nationwide. IMS receives all prescriptions from approximately one-third of stores and a significant sample of prescriptions from many of the remaining stores.

### **IMS, Vector One®: Total Patient Tracker (TPT)**

The IMS, Vector One®: Total Patient Tracker is a national-level projected audit designed to estimate the total number of unique patients across all drugs and therapeutic classes in the retail outpatient setting over time.

TPT derives its data from the Vector One® database, which integrates prescription activity from a sample received from payers, switches, and other software systems that may arbitrage prescriptions at various points in the sales cycle. Vector One® receives over 1.9 billion prescription claims per year, representing over 158 million unique patients. Since 2002 Vector One® has captured information on over 15 billion prescriptions representing over 356 million unique patients.

### **Encuity Research, LLC, Treatment Answers™**

Encuity Research, LLC., Treatment Answers™ and Treatment Answers™ with Pain Panel is a monthly survey designed to provide descriptive information on the patterns and treatment of diseases encountered in office-based physician practices in the U.S. The survey consists of data collected from over 3,200 office-based physicians representing 30 specialties across the United States that report on all patient activity during one typical workday per month. These data may include profiles and trends of diagnoses, patients, drug products mentioned during the office visit and treatment patterns. The Pain Panel supplement surveys over 115 pain specialists physicians each month. With the inclusion of visits to pain specialists, this will allow additional insight into the pain market. The data are then projected nationally by physician specialty and region to reflect national prescribing patterns.

## 8.3 APPENDIX C. DRUG UTILIZATION TABLES AND FIGURES

**Table 1:**

Nationally estimated number of patients, stratified by patient age, with an inpatient or outpatient ER hospital billing for clopidogrel from U.S. non-federal hospitals																						
	2002		2003		2004		2005		2006		2007		2008		2009		2010		2011		2012	
	Patients	Share	Patients	Share	Patients	Share	Patients	Share	Patients	Share	Patients	Share	Patients	Share	Patients	Share	Patients	Share	Patients	Share	Patients	Share
	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
TOTAL PATIENTS	1,765,547	100.0%	2,037,894	100.0%	2,288,903	100.0%	2,289,855	100.0%	2,304,841	100.0%	2,341,596	100.0%	2,367,443	100.0%	2,464,721	100.0%	2,446,368	100.0%	2,270,071	100.0%	2,220,697	100.0%
0-16 years	595	0.03%	678	0.03%	665	0.03%	905	0.04%	823	0.04%	892	0.04%	900	0.04%	1,184	0.05%	763	0.03%	617	0.03%	581	0.03%
< 1 year	272	45.7%	321	47.3%	185	27.8%	277	30.7%	177	21.5%	233	26.1%	236	26.2%	239	20.2%	127	16.7%	41	6.7%	121	20.8%
1-5 years	70	11.8%	112	16.5%	164	24.6%	92	10.2%	193	23.4%	162	18.2%	153	17.0%	302	25.5%	253	33.2%	159	25.7%	128	22.0%
6-16 years	253	42.5%	246	36.2%	316	47.6%	536	59.2%	453	55.1%	502	56.3%	511	56.8%	643	54.3%	383	50.2%	417	67.6%	332	57.2%
17+ years	1,765,016	99.97%	2,037,228	99.97%	2,288,251	99.97%	2,288,940	99.96%	2,304,052	99.97%	2,340,407	99.95%	2,363,200	99.82%	2,463,528	99.95%	2,445,562	99.97%	2,269,442	99.97%	2,220,110	99.97%
Unspecified Age	--	--	--	--	--	--	34	<0.01%	7	<0.01%	348	0.01%	3,355	0.1%	20	<0.01%	49	<0.01%	12	<0.01%	7	<0.01%

\*Unique patient counts may not be added across time periods due to the possibility of double counting those patients who are receiving treatment over multiple periods in the study.

\* Patient age subtotals may not sum exactly due to patients aging during the study ("the cohort effect"), and may be counted more than once in the individual age categories. For this reason, summing across time periods or patient age bands is not advisable and will result in overestimates of patient counts.

Source: IMS, Inpatient Healthcare Utilization System (IHCUS). Years 2002-2012. Extracted March 28, 2013. Files: IHCUS 2013-910, Plavix BPCA by age, 3-28-2013.xls, IHCUS 2013-910, Plavix BPCA 0-16year, 3-28-2013.xls,

**Table 2:**

Nationally estimated number of discharges, stratified by patient age, with an inpatient or outpatient ER hospital billing for clopidogrel from U.S. non-federal hospitals																						
	2002		2003		2004		2005		2006		2007		2008		2009		2010		2011		2012	
	Discharges	Share	Discharges	Share	Discharges	Share	Discharges	Share	Discharges	Share	Discharges	Share	Discharges	Share	Discharges	Share	Discharges	Share	Discharges	Share	Discharges	Share
	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
TOTAL DISCHARGES	2,311,297	100.0%	2,703,009	100.0%	3,088,278	100.0%	3,121,414	100.0%	3,188,734	100.0%	3,288,156	100.0%	3,373,896	100.0%	3,601,235	100.0%	3,650,922	100.0%	3,433,318	100.0%	3,359,494	100.0%
0-16 years	951	0.04%	757	0.03%	692	0.02%	1,060	0.03%	923	0.03%	967	0.03%	1,077	0.03%	1,361	0.04%	909	0.02%	743	0.02%	621	0.02%
< 1 year	272	28.6%	321	42.4%	205	29.6%	285	26.8%	177	19.1%	238	24.6%	326	30.3%	321	23.6%	161	17.7%	41	5.6%	129	20.8%
1-5 years	121	12.7%	119	15.7%	164	23.6%	92	8.7%	193	20.9%	173	17.9%	176	16.4%	337	24.7%	291	32.0%	193	26.0%	141	22.7%
6-16 years	559	58.7%	318	42.0%	324	46.8%	684	64.5%	554	60.0%	555	57.4%	575	53.4%	704	51.7%	457	50.3%	509	68.5%	351	56.5%
17+ years	2,310,346	99.96%	2,702,252	99.97%	3,087,586	99.98%	3,120,321	99.96%	3,187,804	99.97%	3,286,841	99.96%	3,368,850	99.85%	3,599,853	99.96%	3,649,965	99.97%	3,432,564	99.98%	3,358,867	99.98%
Unspecified Age	--	--	--	--	--	--	34	<0.01%	7	<0.01%	348	0.01%	3,969	0.1%	20	<0.01%	49	<0.01%	12	<0.01%	7	<0.01%

Source: IMS, Inpatient Healthcare Utilization System (IHCUS). Years 2002-2012. Extracted March 28, 2013. Files: IHCUS 2013-910, Plavix BPCA by age, 3-28-2013.xls, IHCUS 2013-910, Plavix BPCA 0-16year, 3-28-2013.xls

Figure 1:

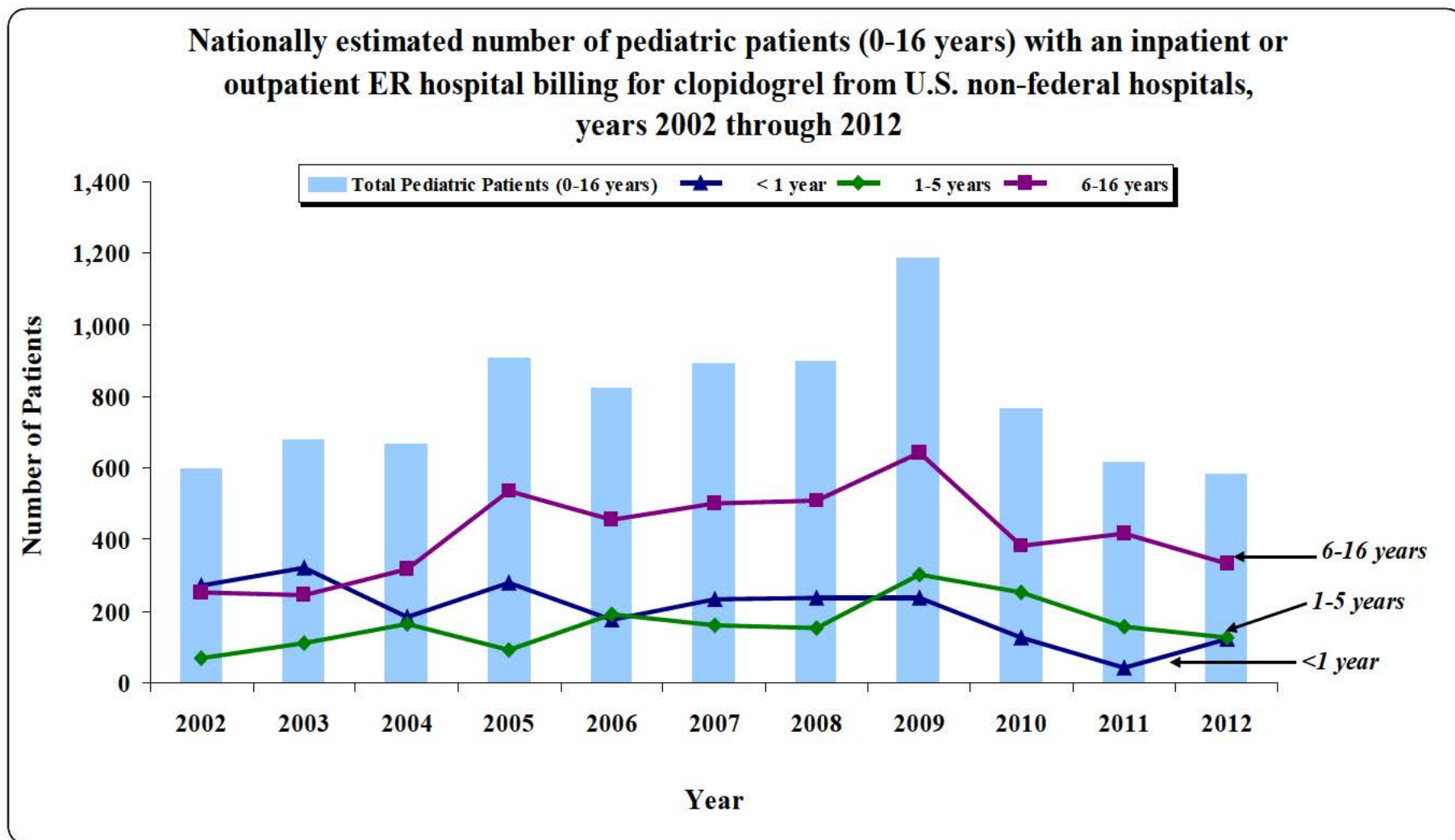


Table 3:

## Nationally estimated number of patients, stratified by patient age, who received a dispensed prescription for a clopidogrel from U.S. outpatient retail pharmacies

	2002		2003		2004		2005		2006		2007		2008		2009		2010		2011		2012	
	Patients N	Share %	Patients N	Share %	Patients N	Share %	Patients N	Share %	Patients N	Share %	Patients N	Share %	Patients N	Share %	Patients N	Share %	Patients N	Share %	Patients N	Share %	Patients N	Share %
<b>TOTAL PATIENTS</b>	<b>2,727,777</b>	<b>100.0%</b>	<b>3,076,454</b>	<b>100.0%</b>	<b>3,543,506</b>	<b>100.0%</b>	<b>3,679,842</b>	<b>100.0%</b>	<b>4,076,534</b>	<b>100.0%</b>	<b>4,411,806</b>	<b>100.0%</b>	<b>4,290,856</b>	<b>100.0%</b>	<b>4,306,746</b>	<b>100.0%</b>	<b>4,569,193</b>	<b>100.0%</b>	<b>4,261,404</b>	<b>100.0%</b>	<b>4,172,881</b>	<b>100.0%</b>
0-16 years	3,092	0.1%	4,649	0.2%	2,994	0.1%	2,949	0.1%	2,801	0.1%	3,140	0.1%	3,489	0.1%	4,189	0.1%	6,580	0.1%	7,421	0.2%	8,622	0.2%
< 1 year	303	9.8%	415	8.9%	313	10.5%	283	9.6%	251	8.9%	194	6.2%	167	4.8%	297	7.1%	417	6.3%	465	6.3%	462	5.4%
1-5 years	1,492	48.2%	2,141	46.0%	1,368	45.7%	1,450	49.2%	1,009	36.0%	892	28.4%	996	28.5%	1,146	27.4%	1,600	24.3%	1,692	22.8%	1,837	21.3%
6-16 years	1,346	43.5%	2,142	46.1%	1,355	45.2%	1,263	42.8%	1,590	56.8%	2,123	67.6%	2,392	68.6%	2,851	68.1%	4,651	70.7%	5,396	72.7%	6,427	74.5%
17+ years	2,719,192	99.7%	3,067,342	99.7%	3,540,007	99.9%	3,676,733	99.9%	4,073,730	99.9%	4,408,730	99.9%	4,287,411	99.9%	4,302,042	99.9%	4,561,289	99.8%	4,253,319	99.8%	4,164,265	99.8%
Unspecified Age	5,599	0.2%	4,771	0.2%	746	0.0%	458	0.0%	197	0.0%	141	0.0%	56	0.0%	1,655	0.0%	3,596	0.1%	1,595	0.0%	198	0.0%

\*Unique patient counts may not be added across time periods due to the possibility of double counting those patients who are receiving treatment over multiple periods in the study.

\*\* Patient age subtotals may not sum exactly due to patients aging during the study ("the cohort effect"), and may be counted more than once in the individual age categories. For this reason, summing across time periods or patient age bands is not advisable and will result in overestimates of patient counts.

Source: IMS, Vector One®: Total Patient Tracker (TPT). Years 2002-2012. Extracted March 28, 2013. Files: TPT 2013-910, Plavix BPCA by age, 3-28-2013.xls, TPT 2013-910, Plavix BPCA 0-16 years by year, 3-28-2013.xls, TPT 2013-910, Plavix BPCA by age Aggregate, 3-28-2013.xls, and TPT

Table 4:

## Nationally estimated number of prescriptions, stratified by patient age, dispensed for clopidogrel from U.S. outpatient retail pharmacies

	2002		2003		2004		2005		2006		2007		2008		2009		2010		2011		2012	
	TRxs N	Share %	TRxs N	Share %	TRxs N	Share %	TRxs N	Share %	TRxs N	Share %	TRxs N	Share %	TRxs N	Share %	TRxs N	Share %	TRxs N	Share %	TRxs N	Share %	TRxs N	Share %
<b>TOTAL PRESCRIPTIONS</b>	<b>10,830,711</b>	<b>100.0%</b>	<b>13,908,586</b>	<b>100.0%</b>	<b>16,976,233</b>	<b>100.0%</b>	<b>18,822,707</b>	<b>100.0%</b>	<b>21,974,214</b>	<b>100.0%</b>	<b>23,907,107</b>	<b>100.0%</b>	<b>25,079,891</b>	<b>100.0%</b>	<b>25,541,503</b>	<b>100.0%</b>	<b>25,003,396</b>	<b>100.0%</b>	<b>23,730,139</b>	<b>100.0%</b>	<b>22,779,685</b>	<b>100.0%</b>
0-16 years	9,764	0.1%	12,134	0.1%	9,384	0.1%	9,327	0.0%	7,543	0.0%	8,399	0.0%	9,972	0.0%	12,069	0.0%	18,572	0.1%	21,367	0.1%	23,691	0.1%
< 1 year	800	8.2%	865	7.1%	854	9.1%	686	7.4%	524	6.9%	426	5.1%	380	3.8%	714	5.9%	868	4.7%	845	4.0%	868	3.7%
1-5 years	6,120	62.7%	6,592	54.3%	5,261	56.1%	4,709	50.5%	2,677	35.5%	2,529	30.1%	3,034	30.4%	3,326	27.6%	4,711	25.4%	4,973	23.3%	4,854	20.5%
6-16 years	2,844	29.1%	4,677	38.5%	3,269	34.8%	3,932	42.2%	4,343	57.6%	5,444	64.8%	6,559	65.8%	8,028	66.5%	12,993	70.0%	15,548	72.8%	17,969	75.8%
17+ years	10,764,632	99.4%	13,814,337	99.3%	16,799,497	99.0%	18,626,281	99.0%	21,966,128	100.0%	23,898,411	100.0%	25,069,771	100.0%	25,521,626	99.9%	24,973,866	99.9%	23,706,511	99.9%	22,755,182	99.9%
Unspecified Age	56,315	0.5%	82,115	0.6%	167,352	1.0%	187,099	1.0%	542	0.0%	297	0.0%	148	0.0%	7,808	0.0%	10,958	0.0%	2,261	0.0%	812	0.0%

Source: IMS, Vector One®: National (VONA). Years 2002-2012. Extracted March 28, 2013. Files: VONA 2013-910, Plavix BPCA by age, 3-28-2013.xls and VONA 2013-910, Plavix BPCA 0-16yrs, 3-28-2013.xls

Figure 2:

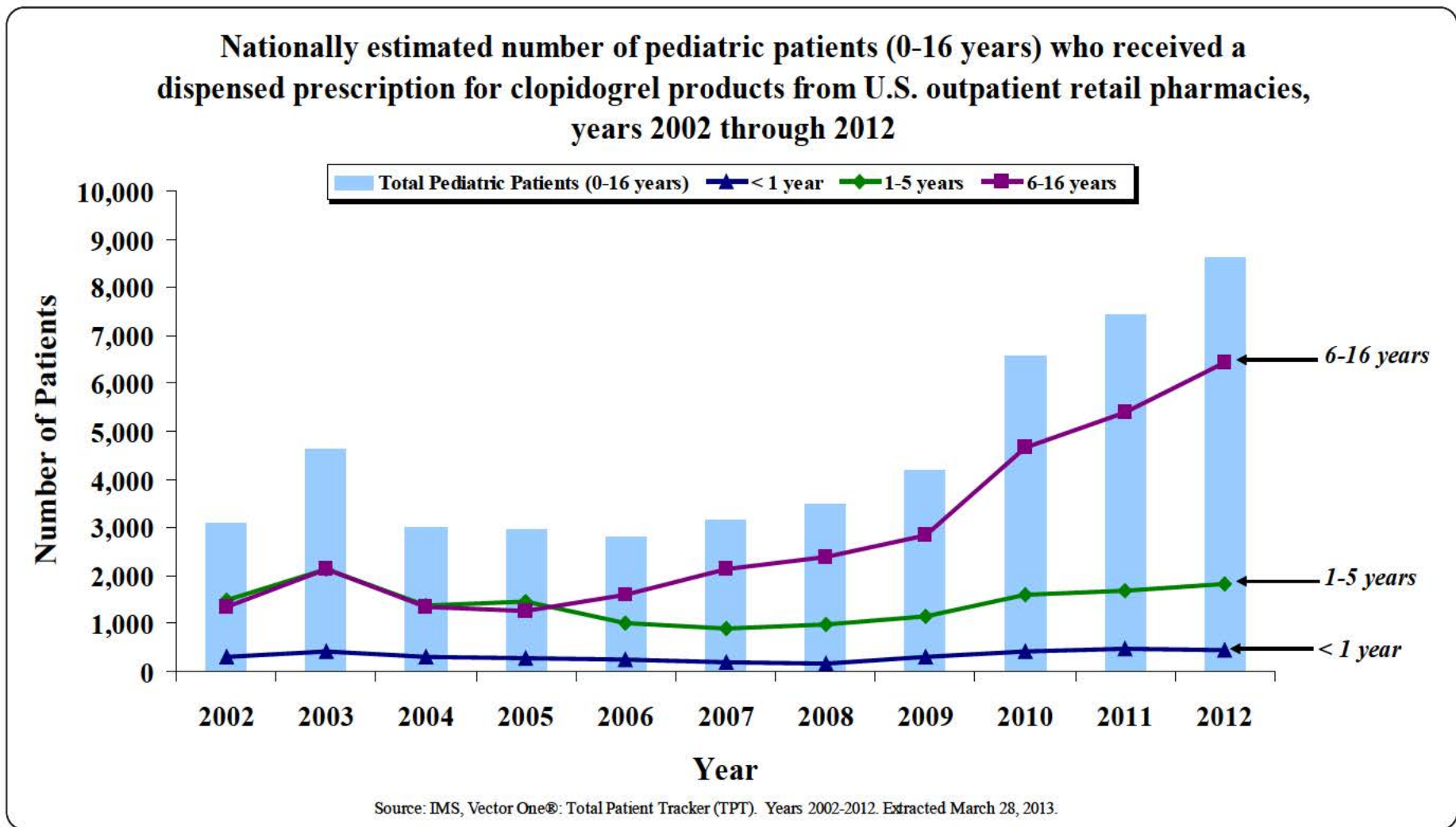


Table 5:

**Top 15 prescribing specialties for clopidogrel by the nationally estimated number of prescriptions dispensed from U.S. outpatient retail pharmacies, from 2002 through 2012, cumulative**

	2002 to 2012	
	TRxs (N)	Share (%)
<b>CLOPIDOGREL TOTAL PRESCRIPTIONS</b>	<b>228,584,461</b>	<b>100.0%</b>
Cardiology	64,240,742	28.1%
Internal Medicine	59,786,098	26.2%
General Practice/Family Medicine/Doctor of Osteopathy	54,205,535	23.7%
Unspecified	14,907,040	6.5%
Nurse Practitioner	5,940,116	2.6%
Neurology	4,197,401	1.8%
Physician Assistant	3,487,204	1.5%
Hospital	3,300,974	1.4%
All Other Surgery	3,050,001	1.3%
Nephrology	1,713,903	0.7%
Pediatrics	1,664,092	0.7%
General Surgery	1,549,748	0.7%
Pulmonary Disease	1,280,940	0.6%
Geriatrics	1,230,503	0.5%
Emergency Medicine	1,053,053	0.5%
All Others	6,977,109	3.1%

Source: IMS, Vector One®: National (VONA). Years 2002-2012. Extracted March 28, 2012. File: VONA 2013-910 Plavix BPCA by specialty, 3-28-2013.xls

Table 6:

**Top diagnoses associated with the use of clopidogrel as reported by U.S. office-based physician surveys, stratified by patient age, from 2002 through 2012, Cumulative**

	2002 to 2012		
	Uses N	Share %	95% Confidence Interval
<b>CLOPIDOGREL TOTAL USES</b>	<b>76,818,000</b>	<b>100.0%</b>	<b>75,505,000 - 78,131,000</b>
<b>6-16 years</b>	29,000	0.0%	3,000 - 54,000
V125 HX CIRCULATORY SYS DIS	19,000	64.6%	<500 - 39,000
4111 INTERMED CORONARY SYND	10,000	35.4%	<500 - 25,000
<b>17 years and older</b>	74,824,000	97.4%	73,528,000 - 76,120,000
4140 CORONARY ATHEROSCLEROSIS	18,788,000	25.1%	18,139,000 - 19,437,000
V125 HX CIRCULATORY SYS DIS	5,845,000	7.8%	5,483,000 - 6,207,000
4439 PERIPH VASCULAR DIS NOS	5,575,000	7.5%	5,221,000 - 5,929,000
4359 TRANS CEREB ISCHEMIA NOS	5,232,000	7.0%	4,889,000 - 5,575,000
V458 OTH POSTSURGICAL STATUS	4,980,000	6.7%	4,646,000 - 5,315,000
4139 ANGINA PECTORIS NEC/NOS	4,682,000	6.3%	4,358,000 - 5,006,000
4360 CVA	3,845,000	5.1%	3,551,000 - 4,138,000
4109 MYOCARDIAL INFARCT NOS	2,830,000	3.8%	2,578,000 - 3,082,000
4019 HYPERTENSION NOS	2,195,000	2.9%	1,973,000 - 2,417,000
4331 CAROTID ARTERY OCCLUSION	1,782,000	2.4%	1,582,000 - 1,982,000
All Others	19,069,000	25.5%	18,415,000 - 19,724,000
<b>Unspecified Age</b>	<b>1,965,000</b>	<b>2.6%</b>	<b>1,755,000 - 2,175,000</b>

*\*The sample size was too low to capture diagnoses codes for the pediatric population aged 0-5 years.*

**\*\*NOS:** not otherwise specified

**\*\*\* Encuity Research LLC, Treatment Answers™** recommends caution interpreting projected annual uses or mentions below 100,000, as the sample size is very small with correspondingly large confidence intervals.

**Source: Encuity Research, LLC, Treatment Answers™.** Years 2002-2012. Extracted March 28, 2013. File PDDA 2013-910 Plavix BPCA by age & 4-Digit DX, 3-28-2013

#### 8.4 APPENDIX D. FAERS CASE SUMMARIES OF FATAL PEDIATRIC CASES (N=4)

VASCULAR (N=4)				
CASE #	SOURCE	AGE	GENDER	SUMMARY
8618432	Foreign	5 months	M	A male was born at 40 weeks gestation with tricuspid and pulmonary atresia and ventricular septal defect (VSD). Echo showed MAPCAs, ASD, tricuspid atresia, two VSD's, small right ventricle, pulmonary atresia and right aortic arch. At 7 weeks, he underwent unifocalization of all MAPCAs. MBTS was performed between the subclavian artery and unifocalized arteries. Pt was discharged with ASA and clopidogrel. At 20 weeks, the pt exhibited dyspnea with O2 sat 75%. Cardiac catheterization confirmed stenosis of the MAPCA over the left bronchus. An additional MBTS to the PA was performed. Clopidogrel was DC'ed prior to surgery, however the operation was postponed because the pt developed viral conjunctivitis. He was taken to surgery 7 days later with an O2 sat of 75%. After thoracotomy, O2 sat fell leading to bradycardia. Occlusion of the previous MBTS was diagnosed. CP resuscitation was performed. The previous shunt was excised and a new central shunt was constructed. Postoperatively, there were concerns regarding neurologic status due to the preceding arrest. EEG showed nonconvulsive status epilepticus. MRI of the brain revealed edema and severe diffuse ischemic damage. The pt died 12 days later.
7193997	US	1.2 months	M	A one-month old male with HLHS was enrolled in CLARINET. The first stage of palliation consisted of Norwood surgery and MBTS. Clopidogrel was started on 09Jul09. Two wks later, the pt experienced tricuspid regurgitation worsening. Cardiac catheterization was performed on (b) (6). Complication occurred at the end of the study during sheath removal in the femoral artery. Ultrasound revealed pseudoaneurysm with a right iliac artery with no distal flow (perforation). The abdomen revealed a mass in the right lower quadrant consistent with a hematoma. Post-procedural hemorrhage was diagnosed. Repair of right common iliac artery psuedoaneurysm with subsequent ligation of iliac artery was required. During surgery bradycardia occurred. No electrical activity was detected; CP resuscitation was started. The pt received chest compression, epinephrine, atropine and cardioversion attempts without improvement. The vessel was ligated. Despite all efforts there was no improvement. Resuscitation was DC'ed and the pt died.
6041545	US	13 months	F	A 13-month female with Shone's anomaly underwent open-heart procedures, was HO with cardiogenic shock and placed on extracorporeal membrane oxygenation (ECMO). The pt was listed for heart transplantation. A Berlin Heart left ventricular assist device (LVAD) was implanted for prolonged support. Postoperatively, heparin and ASA were started for

				anticoagulation. On postoperative day 3, the pt developed fever and systemic vasodilation. On day 9, renal function worsened and she developed thrombocytopenia despite receiving platelet transfusions. A thrombus was observed on the valve of the Berlin Heart, which enlarged after 48 hours, despite administration of clopidogrel. The Berlin Heart was replaced; the explanted device revealed an extensive thrombus. Lab investigations confirmed HIT II syndrome. Heparin was DC'ed and the pt received lepirudin along with ASA and clopidogrel. Lepirudin was DC'ed after development of pulmonary and gastrointestinal hemorrhage. Despite blood product replacement therapy, platelet count continued to fall and lung compliance declined requiring ventilator support. Despite medical resuscitation multiorgan dysfunction was apparent. Care was withdrawn.
8833572	Foreign	2.5 months	M	Literature report of a 2.5-month old male who experienced cerebral hemorrhage following ASA and clopidogrel administration. Outcome was fatal. No additional information is available.

## 8.5 APPENDIX E. SUMMARY OF REMAINING NON-FATAL PEDIATRIC CASES

Table 1 summarizes the *labeled* adverse events in the non-fatal pediatric cases. A hands-on analysis was performed for each of these cases and DPV determined that no new safety issues were identified.

<b>Table 1. Summary of Labeled Adverse Events in the Non-Fatal Pediatric Cases (N=4)</b>					
<b>Event Classification</b>	<b>Adverse Event</b>	<b>N</b>	<b>Indication</b>	<b>Label location*</b>	<b>Comment</b>
Vascular disorders	Hemorrhage	1	Anticoagulation	W/P	General risk of bleed
Vascular disorders	Hemorrhage	1	Coronary stent placement	W/P	General risk of bleed
Nervous system disorders	Confusional state	1	PFO closure	AR	Confusion
Gastrointestinal disorders	Oropharyngeal blistering	2	ASD	AR	Erythema multiforme
	Oropharyngeal pain				Stevens-Johnson syndrome

\* Definitions: BW = Box Warning, C = Contraindications, W/P = Warnings/Precautions, AR = Adverse Reactions, DI = Drug Interactions, OD = Overdosage, SP= Use in Specific Populations, PCI = Patient Counseling Information, MG = Medication Guide

Table 2 summarizes the *unlabeled* adverse events in the non-fatal pediatric cases. A hands-on analysis was performed for each of these cases and DPV determined that no new safety issues were identified

<b>Table 2. Summary of Unlabeled Adverse Events in the Non-Fatal Pediatric Cases (N=10)</b>					
<b>Event Classification</b>	<b>Adverse Event</b>	<b>N</b>	<b>Indication</b>	<b>Comment</b>	
Injury, poisoning and procedural complications	Overdose	1	Suicide attempt	Cardiac arrest (recovered without sequelae)	
Injury, poisoning and procedural complications	Overdose	1	Anticoagulation	No AE reported	
Injury, poisoning and procedural complications	Overdose	1	Cardiac valve replacement	No AE reported	
Injury, poisoning and procedural complications	Accidental exposure	1	Unknown	No AE reported	
Injury, poisoning and procedural complications	Accidental exposure	1	Unknown	No AE reported	
Vascular disorders	Thrombosis in device	1	Cardiac valve replacement		
Vascular disorders	Thrombosis in device	1	Unknown		
Nervous system disorders	Lethargy	1	Shunt thrombosis		
Ear and labyrinth disorders	Unilateral deafness, tinnitus	2	Narrow arteries		
Respiratory, thoracic and mediastinal disorders	Respiratory arrest	1	Unknown		

## 8.6 APPENDIX F. EXCLUDED FAERS CASE SUMMARIES OF PEDIATRIC CASES (N=6)

PREGNANCY, PUERPERIUM AND PERINATAL COMPLICATIONS (N=6)				
CASE #	SOURCE	AGE	GENDER	SUMMARY
6252306	Foreign	0 day	F	A pregnant female with unspecified age and medical hx was treated with indoramin for migraine and with clopidogrel throughout her pregnancy, oxetorone and atorvastatin from the beginning of her pregnancy until the 8th week of amenorrhoea (WA) and enoxaparin from the 34th to the 42nd WA. The pt gave birth on the 42nd WA to a female baby who was born with multiple malformations including type IV oesophageal atresia, imperforate anus and genitalia abnormalities.
6294865	Foreign	0 day	F	A 35-yo female received clopidogrel following a stroke. She was treated with bisoprolol and prednisolone for SLE. Fourteen months later, the pt became pregnant. The pt received prednisolone throughout pregnancy. Clopidogrel was DC'ed ten days before delivery. On (b) (6), a baby girl was born showing a tendency for hypoglycemia. Five months later the baby was in good condition, but no information was available regarding hypoglycaemia or if further episodes occurred.
6294876	US	0 day	M	A 33-yo female with stroke and TIA started clopidogrel on 22Feb03. On 02Sep03 her physician found out that she was pregnant. Clopidogrel and rabeprazole prescribed for her stomach were DC'ed. On 20Sep03 she had numbness in her arm and left side, and her left eye was blurred. On 02Oct03 she was put back on clopidogrel. On 22Oct03 her perinatologist advised her to DC clopidogrel and take heparin. The gynecologist advised her to DC clopidogrel. Despite this, the pt continued clopidogrel until 12Nov03 when it was permanently DC'ed. She was switched to heparin. (b) (6) the pt had an emergency c-section and delivered a premature baby boy at 24 weeks. The baby was put on life support, but developed complications and taken off. The baby died (b) (6)
7239383	Foreign	1 day	M	A male pt was born to a 42-yo mother with PMH of DM and two episodes of MI received the following medications during pregnancy: atorvastatin, ramipril, metformin, insulin, clopidogrel and ASA. Pregnancy was detected 16Sep09 at 31 WA. Clopidogrel, ramipril, atorvastatin, metformin were DC'ed. Allopurinol, ASA and insulin were continued and atenolol and omega 3 acid ethyl esters were started. Ultrasound at week 31 and 32 revealed cerebral redistribution, placental resistance and intra-uterine growth retardation with no oligohydramnios. The baby was delivered by c-section on (b) (6) at 34 WA. On (b) (6)

				<p>the neonate suffered from prematurity, fetal hypotrophy and hypoglycemia. The newborn was small for GA, height, weight and cranial circumference. He presented with respiratory distress syndrome (RDS) on hyaline membrane disease requiring neonatal resuscitation. Renal function work-up revealed spontaneous diuresis, SCr 93mol/l and CrCl of 10 ml/min. Renal ultrasound revealed normal size kidneys relative to the age normal architecture corticomedullary differentiation, no dilation of the pyelocaliceal cavities. There was neonatal jaundice and hypoglycemia. The neonate was discharged on (b) (6). He recovered from hypoglycemia, however prematurity and hypotrophy persisted at the time of the report.</p>
6294883	US	0 day	M	<p>A male newborn weighing "900 gr" was born with bone marrow suppression after his mother took clopidogrel for a stroke during pregnancy. The newborn was HO and received a blood and platelet transfusion. The physician reported bone suppression has resolved.</p>
8152757	US	0 day	F	<p>A female pt with antiphospholipid antibody syndrome and PE received clopidogrel until she found out she was pregnant. Upon detection, clopidogrel was DC'ed and the pt was switched to enoxaparin. The pt delivered a female baby on (b) (6). The baby was born with a toe defect in which all the toes are missing the distal phalanges bone or the last bone in each of her toes. Her toes are short like nubs and none of the toes have toenails. The pt was not taking concomitant medications.</p>

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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AMY I CHEN  
06/05/2013

CAROLYN J TABAK  
06/11/2013

KUSUM S MISTRY  
06/11/2013  
Drug use data has been cleared by the database vendors.

SUSAN LU  
06/12/2013

ALLEN D BRINKER  
06/12/2013

LAURA A GOVERNALE  
06/12/2013

MIN CHU CHEN  
06/12/2013